DETAILED ACTION

The amendment dated 3-9-10 is acknowledged.

Claims included in the prosecution are 42-46.

In view of the amendment, the double patenting rejection is withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 42-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant amends claim 42 to define the drug resistance-modulating agent as one without antineoplastic activity. In view of this amendment it is unclear as to what applicant intends to convey by 'synergistic' or 'synergistic ratio' in said claim. 'Synergism' as defined by Webster's dictionary is "interaction of discrete agencies, agents (as drugs) or conditions such that the total effect is greater than the sum of the individual effects". According to the amendment, the modulator has no antineoplastic activity at all. In such a case, its action is only a potentiating action and there is no synergistic effect, which is a sum of both the neoplastic agent and the modulator.

The meets and bounds of inhibitors for the three components recited in claim 47 are unclear.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 42- 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuo (Journal of controlled Release, 2001) or Krishna (Int. J. Cancer, 2000) or Singh (European Journal of Pharmaceutics and Biopharmaceutics, 2001) or Sadasivan (Cancer Letters, 1991) by themselves or in combination (all are of record) in combination with applicant's statements of prior art record or vice versa.

According to instant claims liposomes have stably associated with first antineoplastic agent and a drug resistance-modulating agent which have amounts which have a synergistic effect. Instant claims do not define what the drug resistance modulating agent is.

Matsuo teaches a method of preparation of liposomes which reverse multi-drug resistance. The liposomes contain vincristine and MRK-16, a monoclonal antibody to P-glycoprotein (see abstract and materials and methods). What is lacking in Matsuo is the teaching of first determining the amounts of vincristine and MRK-16 which are synergistic by an in vitro by Chow-Talalay median effect method and then use those amounts of the active agents in the liposomes.

Krishna teaches increased intracellular drug accumulation and complete chemo sensitization in multidrug-resistant solid tumors by co-administering valspodor (PSC 833) with sterically stabilized liposomal doxorubicin (abstract and materials and methods).

Singh discloses the preparation of stealth monensin immunoliposomes as potentiators of immunotoxins (abstract and materials and methods).

Sadasivan teaches a method of preparation of composition which contains verapamil and liposome encapsulated doxorubicin for the reversal of multi-drug resistance (summary and materials and methods).

Applicant on pages 17 and 18 states that various algorithm methods, Chou-Talalay median effect method to determine the synergistic activity of anti-cancer drugs is known in the art.

Assuming that the amounts of the active agents in Matsuo, Krishna, Singh and Sadasivan are not synergistic, it is deemed obvious to one of ordinary skill in the art to prepare Matsuo's liposomes with amounts of the active agents in synergistic amounts by first determining the synergistic amounts in vitro with a reasonable expectation of success since in vitro determination of the synergistic amounts is well-known in the art as stated by applicant.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the invention requires applying Chou-Talalay median effect method to the combination of antineoplastic agent and a drug resistance modulator and further requires that the synergistic ratio obtained be put into liposomes

to result in coordinated delivery of the synergistic ratio thus determined and none of the cited documents supply these missing elements. This argument is not persuasive. First of all since the modulator has no antineoplastic activity it is unclear as to how one can apply Chou-Talalay model and determine the synergistic effect and then extrapolate it to the in vivo coordinated delivery. Secondly, as pointed out above, Chou-Talalay method to determine the synergistic activity of anti-cancer drugs is known in the art and since this method to be followed up by in vivo administration, it would be obvious to one of ordinary skill in the art to use those amounts of the agents obtained by Chou-Talalay method in the liposomes taught by the prior art cited.

Applicant argues that Matsuo employs vincristine encapsulated in liposomes that are coupled to the tumor targeting agent MRK-16, which also acts as a drug resistance modulator by binding to P-gp and since the MRK-16 is a part of the liposome structure itself, it is difficult to see how the method of the invention could be performed. This argument is perplexing since instant claims recite "stably associating with said liposomes a mole ratio of agents" and thus, does not exclude the stable association of MRK-16 in Matsuo. With regard to applicant's argument that Matsuo lacks any suggestion whatsoever of first determining the amounts of vincristine and MRK-16 that are synergistic in vitro, the examiner points out once again that Chou-Talalay method is meant to be followed up with in vivo administration (no one uses an in vitro method just for the fun of it) and it is within the skill of the art to determine the amount of the modulating agent for maximum potentiation of the antineoplastic effect of vincristine.

Applicant argues that Krishna describes the ability of valspodor to enhance the efficacy of liposomal doxorubicin, but there is no suggestion of determining a synergistic effect over a concentration range, nor is there any suggestion that coordinated pharmacokinetics be assured. Applicant further argues that valspodor was supplied as a free drug and not included in liposomes. Applicant argues that Singh also teaches immunotoxins in free form. Applicant argues that similarly, Sadasivan teaches the verapamil can enhance the uptake of doxorubicin but the verapamil is not encapsulated or associated with liposomes.

These arguments are not persuasive. The same response as above is applicable for applicant's arguments regarding synergism. Krishna basically teaches complete chemo sensitization using co-administration of valspodor and liposomal doxorubicin. Administration of valspodor of Krishna or immunotoxins of Singh or Verapamil of Sadasivan also in liposomes would have been obvious since Matsuo teaches the association of both the modulator and the antineoplastic drug. Encapsulation of two agents in liposomes and encapsulation of a chemotherapeutic agent and a chemo sensitizer in microspheres is well-known in the art of microspheres as evident from Saxon (Journal of Liposome Research, 1999), Vaage (European Journal of Cancer, 1995) and WO 98/50018 which are already of record.

5. Claims 42-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuo (Journal of controlled Release, 2001) or Krishna (Int. J. Cancer, 2000) or Singh (European Journal of Pharmaceutics and Biopharmaceutics, 2001) or Sadasivan (Cancer Letters, 1991) by themselves or in combination (all are of record) in

combination with Giles (US 2003/0083316), Vaage (European Journal of Cancer 1995) and WO 98/50018) of record.

The teachings of Matsuo, Krishna, and Sadasivan have been discussed above.

Giles while disclosing a pharmaceutical combination for the treatment of cancer using OddC and Ara-C teaches first determination of the effect of the combination in CRRF_CEM cells. To determine if the combination is additive, antagonistic or synergistic, a linear cure fitting was used, using the CalcuSyn software which is based on algorithms developed by Chou and Talalay (Examples, Example 3 in particular).

Vaage encapsulation of vincristine and doxorubicin in liposomes (Abstract and Materials and Methods).

WO 98 teaches encapsulation of a chemotherapeutic agent and a chemo sensitizer in microspheres (abstract).

The use of art known algorithms and analysis of the data such as Chou-Talalay median-effect method to determine the non-antagonist ratio and encapsulation of the chemotherapeutic agent and the modulator in liposomes with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since the reference of Giles shows that this method is used to determine the effect is additive, antagonistic or synergistic and the references of Vaage and WO teach encapsulation of two agents in liposomes and microspheres.

4. Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuo (Journal of controlled Release, 2001) or Krishna (Int. J. Cancer, 2000) or Singh

(European Journal of Pharmaceutics and Biopharmaceutics, 2001) or Sadasivan (Cancer Letters, 1991) by themselves or in combination (all are of record) in combination with applicant's statements of prior art record or vice versa ***OR*** as being unpatentable over Matsuo (Journal of controlled Release, 2001) or Krishna (Int. J. Cancer, 2000) or Singh (European Journal of Pharmaceutics and Biopharmaceutics, 2001) or Sadasivan (Cancer Letters, 1991) by themselves or in combination (all are of record) in combination with Giles (US 2003/0083316), Vaage (European Journal of Cancer 1995) and WO 98/50018) of record both as set forth above, further in view of Smith (6,248,752).

The teachings of Matsuo, Krishna, Singh, Sadasivan, Giles, Vaage and WO have been discussed above. What is lacking in these references is the chemo sensitizer or modulator to be an inhibitor of the ATP-binding cassette transporter.

Smith teaches compounds such as azabicyclooctanes enhance the efficacy of anti-cancer drugs by inhibiting the ability of drug transport proteins to efflux therapeutic agents from cells (abstract, col. 8, line 64 through col. 9, line 48).

The use of a modulator such as azabicyclooctanes as the modulator or chemo sensitizer along with the chemotherapeutic drugs taught by Matsuo, Krishna, Singh and Sadasivan would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since the principle of modulating the effect of the chemotherapeutic drug is the same.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S. KISHORE whose telephone number is (571)272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK